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NEWS 4	DEC 18	CA/CAplus patent kind codes updated
NEWS 5	DEC 18	MARPAT to CA/CAplus accession number crossover limit increased to 50,000
NEWS 6	DEC 18	MEDLINE updated in preparation for 2007 reload
NEWS 7	DEC 27	CA/CAplus enhanced with more pre-1907 records
NEWS 8	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
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NEWS 12	JAN 22	CA/CAplus updated with revised CAS roles
NEWS 13	JAN 22	CA/CAplus enhanced with patent applications from India
NEWS 14	JAN 29	PHAR reloaded with new search and display fields
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NEWS 20	FEB 26	EMBASE enhanced with Clinical Trial Number field
NEWS 21	FEB 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS 22	FEB 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS 23	FEB 26	CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
NEWS 24	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS 25	MAR 16	CASREACT coverage extended
NEWS 26	MAR 20	MARPAT now updated daily
NEWS 27	MAR 22	LWPI reloaded
NEWS 28	MAR 30	RDISCLOSURE reloaded with enhancements
NEWS 29	MAR 30	INPADOCDB will replace INPADOC on STN
NEWS 30	APR 02	JICST-EPLUS removed from database clusters and STN

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=> s screening
L1     1048993 SCREENING

=> s l1 and detecting
L2       32850 L1 AND DETECTING

=> s l2 and tumor metastasis
L3          21 L2 AND TUMOR METASTASIS

=> s l3 and anti-VEGF-D
L4           0 L3 AND ANTI-VEGF-D

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L5           0 L2 AND ANTI-VEGF-D

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L8           3 L6 AND VEGF-D

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L9           3 DUP REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 1-3 cbib abs

L9   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
2003:282828   Document No. 138:298132  Modulators of VEGF or VEGFR binding to
     neuropilin-2, materials and methods for detecting said
     modulators, and therapeutic uses of the modulators..  Alitalo, Kari;
     Karkkainen, Marika; Karila, Kaisa (Ludwig Institute for Cancer Research,
     USA; Licentia Ltd.).  PCT Int. Appl. WO 2003029814 A2 20030410, 181 pp.
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DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-EP11069 20021001. PRIORITY: US 2001-326326P 20011001.

AB The present invention relates to identifying modulators of VEGF-C binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGF-C polypeptide is claimed comprising steps of: (a) contacting a neuropilin composition with a VEGF-C composition, in the presence and in the absence of a putative modulator compound; (b) detecting binding between the neuropilin polypeptide and the VEGF-C polypeptide in the presence and absence of the putative modulator compound; and (c) identifying a modulator compound based on a decrease or increase in binding in the presence of the putative modulator compound as compared to binding in the absence of the putative modulator compound The neuropilin receptor composition comprises a neuropilin receptor extracellular domain fragment bound to a solid support or a neuropilin receptor extracellular domain fragment fused to an Ig Fc fragment. The VEGF-C composition comprises a purified mammalian prepro-VEGF-C polypeptide or a fragment. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGFR-3 polypeptide is also claimed. The VEGFR-3 composition used in the method comprises a receptor extracellular domain fragment bound to a solid support or a receptor extracellular domain fragment fused to an Ig Fc fragment. Addnl. claimed is a method for screening for selectivity of a modulator of VEGF-C, VEGFR, or neuropilin biol. activity. A method of modulating growth, migration, or proliferation of cells, specifically neurons, in a mammalian organism by administering a composition comprising a neuropilin polypeptide or fragment, and a VEGF, a PlGF, a semaphorin, or a bispecific antibody specific for the neuropilin receptor and for a VEGF-C polypeptide or for a neuropilin receptor and a VEGFR is also claimed.

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

2002:575554 Document No. 137:135068 Methods for treating neoplastic disease characterized by vascular endothelial growth factor D expression, for screening for neoplastic disease or metastatic risk, and for maintaining vascularization of tissue. Achen, Marc; Stacker, Steven (Australia). U.S. Pat. Appl. Publ. US 2002102260 A1 20020801, 45 pp., Cont.-in-part of U.S. Ser. No. 796,714. (English). CODEN: USXXCO. APPLICATION: US 2001-956095 20010920. PRIORITY: US 2000-186361P 20000302; US 2000-234196P 20000920; US 2001-796714 20010302.

AB A method for treating and alleviating disease characterized by the expression of VEGF-D involving screening to find an organism with tumor cells expressing VEGF-D and administering an effective amount of a VEGF-D antagonist; a method for screening for neoplastic disease, where detection of VEGF-D on or in a sample such as tumor cells, blood vessel endothelial cells or lymph vessel endothelial cells indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism involving administering a vascularization promoting amount of VEGF-D or a fragment or analog thereof to the organism; a method for screening tumors for metastatic risk involving detecting expression of VEFG-D by a tumor which indicates metastatic risk; and a method of detecting micro-metastasis of neoplastic disease involving detection of VEGF -D on or in a tissue sample which indicates metastasis of a neoplastic disease.

L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2001:661270 Document No. 135:205534 Methods for treating, screening for, and detecting cancers expressing vascular endothelial growth factor D (VEGF-D). Achen, Marc; Stacker, Steven (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001064235 A1 20010907, 78 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US6791 20010302. PRIORITY: US 2000-PV186361 20000302.

AB A method for treating and alleviating melanomas and various cancers characterized by the expression of VEGF-D by the tumor comprises screening to find an organism with tumor cells expressing VEGF-D and administering an effective amount of a VEGF-D antagonist to prevent binding of VEGF-D. Also provided are methods for screening for neoplastic diseases, where detection of VEGF-D on or in cells such as tumor cells, blood vessel endothelial cells, lymph vessel endothelial cells, and/or cells with potential neoplastic growth indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism by administering VEGF-D or a fragment or analog thereof; methods for screening tumors for metastatic risk where expression of VEGF-D by the tumor indicates metastatic risk; and methods to detect micro-metastasis of neoplastic disease where detection of VEGF-D on or in a tissue sample indicates metastasis of neoplastic disease.

=> s detect?
L10 5876906 DETECT?

=> s l10 and VEGF-D
L11 285 L10 AND VEGF-D

=> s l11 and unprocessed VEGF_D
L12 5 L11 AND UNPROCESSED VEGF_D

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PROCESSING COMPLETED FOR L12
L13 1 DUP REMOVE L12 (4 DUPLICATES REMOVED)

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L13 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
2000011413. PubMed ID: 10542248. Biosynthesis of vascular endothelial growth factor-D involves proteolytic processing which generates non-covalent homodimers. Stacker S A; Stenvers K; Caesar C; Vitali A; Domagala T; Nice E; Roufail S; Simpson R J; Moritz R; Karpanen T; Alitalo K; Achen M G. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia.. steven.stacker@ludwig.edu.au) . The Journal of biological chemistry, (1999 Nov 5) Vol. 274, No. 45, pp. 32127-36. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D) binds and activates the endothelial cell tyrosine kinase receptors VEGF receptor-2 (VEGFR-2) and VEGF receptor-3 (VEGFR-3), is mitogenic for endothelial cells, and shares structural homology and receptor specificity with VEGF-C. The primary translation product of VEGF-D has long N- and C-terminal polypeptide extensions in addition to a central VEGF homology domain (VHD). The VHD of VEGF-D is sufficient to bind and activate VEGFR-2 and VEGFR-3. Here we report that VEGF-D is proteolytically processed to release the VHD. Studies in 293EBNA cells demonstrated that VEGF-D undergoes N- and C-terminal cleavage events to produce numerous secreted polypeptides including a fully processed form of M(r) approximately 21,000 consisting only of the VHD, which is predominantly a non-covalent dimer. Biosensor analysis demonstrated that the VHD has approximately 290- and approximately 40-fold greater affinity for VEGFR-2 and VEGFR-3, respectively, compared with unprocessed VEGF-D . In situ hybridization demonstrated that embryonic lung is a major site of expression of the VEGF-D gene. Processed forms of VEGF-D were detected in embryonic lung indicating that VEGF-D is proteolytically processed in vivo.

=> s (achen m?/au or stacker s?/au)
L14 529 (ACHEN M?/AU OR STACKER S?/AU)

=> s l14 and VEGF-D
L15 179 L14 AND VEGF-D

=> s l15 and anti-VEGF-D
L16 9 L15 AND ANTI-VEGF-D

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PROCESSING COMPLETED FOR L16
L17 5 DUP REMOVE L16 (4 DUPLICATES REMOVED)

=> d l17 1-5 cbib abs

L17 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2007:12833 Document No.: PREV200700018332. Antibodies to truncated VEGF-D and uses thereof. Anonymous; Achen, Marc G. [Inventor]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 07097986 20060829. Official Gazette of the United States Patent and Trademark Office Patents, (AUG 29 2006)
CODEN: OGUPE7. ISSN: 0098-1133. Language: English.
AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR-2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L17 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1026912 Document No. 143:304651 Chimeric and humanized anti-VEGF-D antibodies and methods of use for modulating angiogenesis and lymphangiogenesis. Achen, Marc G.; Stacker, Stephen; Renner, Christoph (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2005087177 A2 20050922, 126 pp.
DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM;

RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US7283 20050307. PRIORITY: US 2004-550441P 20040305.

AB The present invention relates to materials and methods for modulating angiogenesis and lymphangiogenesis. The compns. of the invention provide chimeric and/or humanized anti-VEGF-D (vascular endothelial growth factor D) antibody substances, antibodies, polypeptides and fragments thereof useful for modulating angiogenesis and lymphangiogenesis in a subject. In one aspect, the anti-VEGF-D antibody comprises complementarity determining regions (CDR) from a mouse antibody and framework regions (FR) from a non-murine (such as human) source. In another aspect, antibody regions have been altered by amino acid substitution to be more homologous to a human antibody sequence. Provided are protein and DNA sequences for VEGF-D antibody substances.

L17 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2002:334517 Document No.: PREV200200334517. Antibodies to truncated VEGF-D and thereof. Achen, Marc G. [Inventor, Reprint author]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6383484 20020507. Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR-2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L17 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2001:112744 Document No.: PREV200100112744. VEGF-D promotes the metastatic spread of tumor cells via the lymphatics. Stacker, Steven A. [Reprint author]; Caesar, Carol; Baldwin, Megan E.; Thornton, Gillian E.; Williams, Richard A.; Prevo, Remko; Jackson, David G.; Nishikawa, Shin-Ichi; Kubo, Hajime; Achen, Marc G.. Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Melbourne, VIC, Australia. steven.stacker@ludwig.edu.au. Nature Medicine, (February, 2001) Vol. 7, No. 2, pp. 186-191. print. ISSN: 1078-8956. Language: English.

AB Metastasis to local lymph nodes via the lymphatic vessels is a common step in the spread of solid tumors. To investigate the molecular mechanisms underlying the spread of cancer by the lymphatics, we examined the ability of vascular endothelial growth factor (VEGF)-D, a ligand for the lymphatic growth factor receptor VEGFR-3/Flt-4, to induce formation of lymphatics in a mouse tumor model. Staining with markers specific for lymphatic endothelium demonstrated that VEGF-D induced the formation of lymphatics within tumors. Moreover, expression of VEGF-D in tumor cells led to spread of the tumor to lymph nodes, whereas expression of VEGF, an angiogenic growth factor which activates VEGFR-2 but not VEGFR-3, did not. VEGF-D also promoted tumor angiogenesis and growth. Lymphatic spread induced by VEGF-D could be blocked with an antibody specific for VEGF-D. This study demonstrates that lymphatics can be established in solid tumors and implicates VEGF family members in determining the route of metastatic spread.

L17 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 1

2000247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF

receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) Vol. 267, No. 9, pp. 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-(VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D .

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=> s l14 and antibod?
L18        139 L14 AND ANTIBOD?

=> s l18 and VEGF-D
L19         52 L18 AND VEGF-D

=> s l19 and VEGFR-2
L20         36 L19 AND VEGFR-2

=> s l20 and VEGFR-3
L21         36 L20 AND VEGFR-3

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L22          16 DUP REMOVE L21 (20 DUPLICATES REMOVED)

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L22  ANSWER 1 OF 16  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
2007:12833  Document No.: PREV200700018332. Antibodies to truncated
     VEGF-D and uses thereof. Anonymous; Achen, Marc
     G. [Inventor]; Stacker, Steven Alan [Inventor]. Parkville,
     Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.:
     US 07097986 20060829. Official Gazette of the United States Patent and
     Trademark Office Patents, (AUG 29 2006)
     CODEN: OGUPE7. ISSN: 0098-1133. Language: English.
AB   The invention is based on the isolation of antibodies that were
     made to a polypeptide having the amino acid sequence for a truncated
     VEGF-D.  One of these antibodies can interfere
     with the activity of VEGF-D mediated by VEGFR
     -2 and interfere with the binding of VEGF-D
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to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L22 ANSWER 2 OF 16 MEDLINE on STN DUPLICATE 1

2006451923. PubMed ID: 16877368. Lymphangiogenic growth factor responsiveness is modulated by postnatal lymphatic vessel maturation. Karpanen Terhi; Wirzenius Maria; Makinen Taija; Veikkola Tanja; Haisma Hidde J; Achen Marc G; Stacker Steven A; Pytowski Bronislaw; Yla-Herttuala Seppo; Alitalo Kari. (Molecular/Cancer Biology Laboratory, Biomedicum Helsinki, P.O.B. 63 (Haartmaninkatu 8), FI-00014 University of Helsinki, Finland.) The American journal of pathology, (2006 Aug) Vol. 169, No. 2, pp. 708-18. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.

AB Lymphatic vessel plasticity and stability are of considerable importance when attempting to treat diseases associated with the lymphatic vasculature. Development of lymphatic vessels during embryogenesis is dependent on vascular endothelial growth factor (VEGF)-C but not VEGF-D. Using a recombinant adenovirus encoding a soluble form of their receptor VEGFR-3 (AdVEGFR-3-Ig), we studied lymphatic vessel dependency on VEGF-C and VEGF-D induced VEGFR-3 signaling in postnatal and adult mice. Transduction with AdVEGFR-3-Ig led to regression of lymphatic capillaries and medium-sized lymphatic vessels in mice under 2 weeks of age without affecting collecting lymphatic vessels or the blood vasculature. No effect was observed after this period. The lymphatic capillaries of neonatal mice also regressed partially in response to recombinant VEGFR-3-Ig or blocking antibodies against VEGFR-3, but not to adenovirus-encoded VEGFR-2-Ig. Despite sustained inhibitory VEGFR-3-Ig levels, lymphatic vessel regrowth was observed at 4 weeks of age. Interestingly, whereas transgenic expression of VEGF-C in the skin induced lymphatic hyperplasia even during embryogenesis, similar expression of VEGF-D resulted in lymphangiogenesis predominantly after birth. These results indicate considerable plasticity of lymphatic vessels during the early postnatal period but not thereafter, suggesting that anti-lymphangiogenic therapy can be safely applied in adults.

L22 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

2005:1260640 Document No. 144:17173 Method for inhibiting angiogenesis and/or lymphangiogenesis. Mccoll, Bradley; Stacker, Steven; Achen, Marc (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2005112971 A1 20051201, 38 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US17639 20050520. PRIORITY: US 2004-572469P 20040520.

AB Proprotein convertase inhibitor has been found to dock proteolytic processing and activation of VEGF-C and VEGF-D and inhibit angiogenesis and/or lymphangiogenesis. Method and composition are disclosed for inhibiting angiogenesis and/or lymphangiogenesis, and for treating conditions associated with excessive angiogenesis, such as tumors and/or retinopathies, as well as conditions associated with lymphangiogenesis, such as the metastatic spread of malignancies, macular degeneration, inflammatory mediated diseases, rheumatoid arthritis, diabetic retinopathy and psoriasis in a patient. The inventive method and composition utilize proprotein convertase antagonist selected from the group consisting of an anti-proprotein convertase antibody, an

antisense nucleic acid mol. against a polynucleotide coding for a proprotein convertase, and an siRNA for inhibiting proprotein convertase expression, as well as proprotein convertase inhibitors.

L22 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1026969 Document No. 143:324792 Multivalent antibodies specific to growth factors of VEGF/PDGF family for diagnosis and treatment of fibrosis, inflammation, cancer and other diseases associated with aberrant angiogenesis. Eriksson, Ulf; Alitalo, Kari; Achen, Marc G.; Renner, Christoph; Stacker, Stephen; Li, Hong; Laakkonen, Pirjo (Ludwig Institute for Cancer Research, USA; Licentia Ltd.). PCT Int. Appl. WO 2005087812 A1 20050922, 152 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US7742 20050307. PRIORITY: US 2004-550511P 20040305; US 2004-586662P 20040709.

AB The present invention relates to materials and methods for modulating angiogenesis. The compns. of the invention provide antibody substances specific for two or more PDGF/VEGF family members, which are useful for modulating angiogenesis and lymphangiogenesis in a subject.

L22 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1026912 Document No. 143:304651 Chimeric and humanized anti-VEGF-D antibodies and methods of use for modulating angiogenesis and lymphangiogenesis. Achen, Marc G.; Stacker, Stephen; Renner, Christoph (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2005087177 A2 20050922, 126 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US7283 20050307. PRIORITY: US 2004-550441P 20040305.

AB The present invention relates to materials and methods for modulating angiogenesis and lymphangiogenesis. The compns. of the invention provide chimeric and/or humanized anti-VEGF-D (vascular endothelial growth factor D) antibody substances, antibodies, polypeptides and fragments thereof useful for modulating angiogenesis and lymphangiogenesis in a subject. In one aspect, the anti-VEGF-D antibody comprises complementarity determining regions (CDR) from a mouse antibody and framework regions (FR) from a non-murine (such as human) source. In another aspect, antibody regions have been altered by amino acid substitution to be more homologous to a human antibody sequence. Provided are protein and DNA sequences for VEGF-D antibody substances.

L22 ANSWER 6 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2004:265559 Document No.: PREV200400271525. Antibodies to truncated VEGF-D and uses thereof. Achen, Marc G. [Inventor, Reprint Author]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6730489 20040504. Official Gazette of the United States Patent and Trademark Office Patents, (May 4 2004) Vol. 1282, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.

AB The invention is based on the isolation of antibodies that were

made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR -2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L22 ANSWER 7 OF 16 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2003224307 EMBASE VEGF-D is the strongest angiogenic and lymphangiogenic effector among VEGFs delivered into skeletal muscle via adenoviruses. Rissanen T.T.; Markkanen J.E.; Gruchala M.; Heikura T.; Puranen A.; Kettunen M.I.; Kholova I.; Kauppinen R.A.; Achen M.G. ; Stacker S.A.; Alitalo K.; Yla-Herttuala S.. Dr. S. Yla-Herttuala, Department of Biotechnology, A.I. Virtanen Institute, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland. Seppo.Ylaherttuala@uku.fi. Circulation Research Vol. 92, No. 10, pp. 1098-1106 30 May 2003.
Refs: 39.
ISSN: 0009-7330. CODEN: CIRUAL
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20030626. Last Updated on STN: 20030626

AB Optimal angiogenic and lymphangiogenic gene therapy requires knowledge of the best growth factors for each purpose. We studied the therapeutic potential of human vascular endothelial growth factor (VEGF) family members VEGF-A, VEGF-B, VEGF-C, and VEGF-D as well as a VEGFR-3-specific mutant (VEGF-C(156S)) using adenoviral gene transfer in rabbit hindlimb skeletal muscle. The significance of proteolytic processing of VEGF-D was explored using adenoviruses encoding either full-length or mature (ΔNΔC) VEGF-D. Adenoviruses expressing potent VEGFR-2 ligands, VEGF-A and VEGF-D(ΔNΔC), induced the strongest angiogenesis and vascular permeability effects as assessed by capillary vessel and perfusion measurements, modified Miles assay, and MRI. The most significant feature of angiogenesis induced by both VEGF-A and VEGF-D(ΔNΔC) was a remarkable enlargement of microvessels with efficient recruitment of pericytes suggesting formation of arterioles or venules. VEGF-A also moderately increased capillary density and created glomeruloid bodies, clusters of tortuous vessels, whereas VEGF-D(ΔNΔC)-induced angiogenesis was more diffuse. Vascular smooth muscle cell proliferation occurred in regions with increased plasma protein extravasation, indicating that arteriogenesis may be promoted by VEGF-A and VEGF-D (ΔNΔC). Full-length VEGF-C and VEGF-D induced predominantly and the selective VEGFR-3 ligand VEGF-C(156S) exclusively lymphangiogenesis. Unlike angiogenesis, lymphangiogenesis was not dependent on nitric oxide. The VEGFR-1 ligand VEGF-B did not promote either angiogenesis or lymphangiogenesis. Finally, we found a positive correlation between capillary size and vascular permeability. This study compares, for the first time, angiogenesis and lymphangiogenesis induced by gene transfer of different human VEGFs, and shows that VEGF-D is the most potent member when delivered via an adenoviral vector into skeletal muscle.

L22 ANSWER 8 OF 16 MEDLINE on STN DUPLICATE 2

2003477107. PubMed ID: 14553837. Vascular endothelial growth factor-D expression in human atherosclerotic lesions. Rutanen Juha; Leppanen Pia; Tuomisto Tiina T; Rissanen Tuomas T; Hiltunen Mikko O; Vajanto Ismo; Niemi Mari; Hakkinen Tomi; Karkola Kari; Stacker Steven A; Achen Marc G; Alitalo Kari; Yla-Herttuala Seppo. (Department of Molecular Medicine, AI Virtanen Institute, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland.) Cardiovascular research, (2003 Oct 1) Vol.

59, No. 4, pp. 971-9. Journal code: 0077427. ISSN: 0008-6363. Pub. country: Netherlands. Language: English.

AB OBJECTIVE: Vascular endothelial growth factor-D (VEGF-D) is a recently characterized member of the VEGF family, but its expression in atherosclerotic lesions remains unknown. We studied the expression of VEGF-D and its receptors (VEGFR -2 and VEGFR-3) in normal and atherosclerotic human arteries, and compared that to the expression pattern of VEGF-A. METHODS: Human arterial samples (n=39) obtained from amputation operations and fast autopsies were classified according to the stage of atherosclerosis and studied by immunohistochemistry. The results were confirmed by in situ hybridization and RT-PCR. RESULTS: We found that while VEGF-A expression increased during atherogenesis, VEGF -D expression remained relatively stable only decreasing in complicated lesions. In normal arteries and in early lesions VEGF -D was mainly expressed in smooth muscle cells, whereas in complicated atherosclerotic lesions the expression was most prominent in macrophages and also colocalized with plaque neovascularization. By comparing the staining profiles of different antibodies, we found that proteolytic processing of VEGF-D was efficient in the vessel wall. VEGFR-2, but not VEGFR-3, was expressed in the vessel wall at every stage of atherosclerosis. CONCLUSIONS: Our results suggest that in large arteries VEGF-D is mainly expressed in smooth muscle cells and that it may have a role in the maintenance of vascular homeostasis. However, in complicated lesions it was also expressed in macrophages and may contribute to plaque neovascularization. The constitutive expression of VEGFR-2 in arteries suggests that it may be one of the principal mediators of the VEGF -D effects in large arteries.

L22 ANSWER 9 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2002:334517 Document No.: PREV200200334517. Antibodies to truncated VEGF-D and thereof. Achen, Marc G. [Inventor, Reprint author]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6383484 20020507. Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR -2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L22 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN

2002:575554 Document No. 137:135068 Methods for treating neoplastic disease characterized by vascular endothelial growth factor D expression, for screening for neoplastic disease or metastatic risk, and for maintaining vascularization of tissue. Achen, Marc; Stacker, Steven (Australia). U.S. Pat. Appl. Publ. US 2002102260 A1 20020801, 45 pp., Cont.-in-part of U.S. Ser. No. 796,714. (English). CODEN: USXXCO. APPLICATION: US 2001-956095 20010920. PRIORITY: US 2000-186361P 20000302; US 2000-234196P 20000920; US 2001-796714 20010302.

AB A method for treating and alleviating disease characterized by the expression of VEGF-D involving screening to find an organism with tumor cells expressing VEGF-D and administering an effective amount of a VEGF-D antagonist; a method for screening for neoplastic disease, where detection of VEGF-D on or in a sample such as tumor cells, blood

vessel endothelial cells or lymph vessel endothelial cells indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism involving administering a vascularization promoting amount of VEGF-D or a fragment or analog thereof to the organism; a method for screening tumors for metastatic risk involving detecting expression of VEFG-D by a tumor which indicates metastatic risk; and a method of detecting micro-metastasis of neoplastic disease involving detection of VEGF-D on or in a tissue sample which indicates metastasis of a neoplastic disease.

L22 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
2001:724562 Document No. 136:32077 Isolated lymphatic endothelial cells transduce growth, survival and migratory signals via the VEGF-C/D receptor VEGFR-3. Makinen, Taija; Veikkola, Tanja; Mustjoki, Satu; Karpanen, Terhi; Catimel, Bruno; Nice, Edouard C.; Wise, Lyn; Mercer, Andrew; Kowalski, Heinrich; Kerjaschki, Dontscho; Stacker, Steven A.; Achen, Marc G.; Alitalo, Kari (Molecular/Cancer Biology Laboratory and Ludwig Institute for Cancer Research, Haartman Institute and Helsinki University Hospital, Biomedicum Helsinki, University of Helsinki, Helsinki, FIN-00014, Finland). EMBO Journal, 20(17), 4762-4773 (English) 2001. CODEN: EMJODG. ISSN: 0261-4189. Publisher: Oxford University Press.

AB Vascular endothelial growth factor receptor-3 (VEGFR-3 /Flt4) binds two known members of the VEGF ligand family, VEGF-C and VEGF-D, and has a critical function in the remodelling of the primary capillary vasculature of midgestation embryos. Later during development, VEGFR-3 regulates the growth and maintenance of the lymphatic vessels. In the present study, the authors have isolated and cultured stable lineages of blood vascular and lymphatic endothelial cells from human primary microvascular endothelium by using antibodies against the extracellular domain of VEGFR-3. The authors show that VEGFR-3 stimulation alone protects the lymphatic endothelial cells from serum deprivation-induced apoptosis and induces their growth and migration. At least some of these signals are transduced via a protein kinase C-dependent activation of the p42/p44 MAPK signaling cascade and via a wortmannin-sensitive induction of Akt phosphorylation. These results define the critical role of VEGF-C/VEGFR-3 signaling in the growth and survival of lymphatic endothelial cells. The culture of isolated lymphatic endothelial cells should now allow further studies of the mol. properties of these cells.

L22 ANSWER 12 OF 16 MEDLINE on STN DUPLICATE 3
2001212643. PubMed ID: 11175849. VEGF-D promotes the metastatic spread of tumor cells via the lymphatics. Stacker S A ; Caesar C; Baldwin M E; Thornton G E; Williams R A; Prevo R; Jackson D G; Nishikawa S; Kubo H; Achen M G. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.) Nature medicine, (2001 Feb) Vol. 7, No. 2, pp. 186-91. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Metastasis to local lymph nodes via the lymphatic vessels is a common step in the spread of solid tumors. To investigate the molecular mechanisms underlying the spread of cancer by the lymphatics, we examined the ability of vascular endothelial growth factor (VEGF)-D, a ligand for the lymphatic growth factor receptor VEGFR-3 /Flt-4, to induce formation of lymphatics in a mouse tumor model. Staining with markers specific for lymphatic endothelium demonstrated that VEGF-D induced the formation of lymphatics within tumors. Moreover, expression of VEGF-D in tumor cells led to spread of the tumor to lymph nodes, whereas expression of VEGF, an angiogenic growth factor which activates VEGFR-2 but not VEGFR-3, did not. VEGF-D also promoted tumor angiogenesis and growth. Lymphatic spread induced by VEGF-D could be blocked with an antibody specific for VEGF-D. This study demonstrates that

lymphatics can be established in solid tumors and implicates VEGF family members in determining the route of metastatic spread.

L22 ANSWER 13 OF 16 MEDLINE on STN DUPLICATE 4
2001156199. PubMed ID: 11180159. Localization of vascular endothelial growth factor-D in malignant melanoma suggests a role in tumour angiogenesis. Achen M G; Williams R A; Minekus M P; Thornton G E; Stenvers K; Rogers P A; Lederman F; Roufail S; Stacker S A. (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050, Australia.. Marc.achen@ludwig.edu.au) . The Journal of pathology, (2001 Feb) Vol. 193, No. 2, pp. 147-54. Journal code: 0204634. ISSN: 0022-3417. Pub. country: England: United Kingdom. Language: English.

AB Expression of angiogenic and lymphangiogenic factors by tumours may influence the route of metastatic spread. Vascular endothelial growth factor (VEGF) is a regulator of tumour angiogenesis, but studies of the inhibition of solid tumour growth by neutralizing anti-VEGF antibodies indicated that other angiogenic factors may be involved. VEGF-D may be an alternative regulator because like VEGF it is angiogenic and it activates VEGF receptor-2 (VEGFR-2), an endothelial cell receptor which is a key signalling molecule in tumour angiogenesis. This study reports the generation of monoclonal antibodies to the receptor-binding domain of VEGF-D and the use of these antibodies to localize VEGF-D in malignant melanoma. VEGF-D was detected in tumour cells and in vessels adjacent to immunopositive tumour cells, but not in vessels distant from the tumours. These findings are consistent with a model in which VEGF-D, secreted by tumour cells, activates endothelial cell receptors and thereby contributes to the regulation of tumour angiogenesis and possibly lymphangiogenesis. In addition, VEGF-D was detected in the vascular smooth muscle, but not the endothelium, of vessels in adult colon. The endothelium of these vessels was negative for VEGFR-2 and VEGFR-3. As VEGF receptors can be up-regulated on endothelium in response to vessel damage and ischaemia, these findings of a specific localization of VEGF-D in smooth muscle of the blood vessels suggest that VEGF-D produced by vascular smooth muscle could play a role in vascular repair by stimulating the proliferation of endothelial cells.

L22 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2007 ACS on STN
2000:441581 Document No. 133:72945 Antibodies to truncated VEGF-D and uses thereof. Achen, Marc G.; Stacker, Steven Alan (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2000037025 A2 20000629, 44 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US31332 19991221. PRIORITY: US 1998-PV113254 19981221; US 1999-PV134556 19990517.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR-2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The antibodies, antibody fragments or compns. containing the antibodies are useful for diagnosis, prognosis, and therapy of VEGF-D or VEGF-C related diseases, e.g. cancer, diabetic retinopathy, psoriasis, arthropathy, fluid accumulation in the heart and/or lung.

L22 ANSWER 15 OF 16 MEDLINE on STN DUPLICATE 5
2000247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) Vol. 267, No. 9, pp. 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-(VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D.

L22 ANSWER 16 OF 16 MEDLINE on STN
2001021068. PubMed ID: 11023993. VEGF-C and VEGF-D expression in neuroendocrine cells and their receptor, VEGFR-3, in fenestrated blood vessels in human tissues. Partanen T A; Arola J; Saaristo A; Jussila L; Ora A; Miettinen M; Stacker S A; Achen M G; Alitalo K. (Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, University of Helsinki, 00014 Helsinki, Finland.) The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2000 Oct) Vol. 14, No. 13, pp. 2087-96. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB Recently, vascular endothelial growth factor receptor 3 (VEGFR-3) has been shown to provide a specific marker for lymphatic endothelia in certain human tissues. In this study, we have investigated the expression of VEGFR-3 and its ligands VEGF-C and VEGF-D in fetal and adult tissues. VEGFR-3 was consistently detected in the endothelium of lymphatic vessels such as the thoracic duct, but fenestrated capillaries of several organs including the bone marrow, splenic and hepatic sinusoids, kidney glomeruli and endocrine glands also expressed this receptor. VEGF-C and VEGF-D, which bind both VEGFR-2 and VEGFR-3 were expressed in vascular smooth muscle cells. In addition, intense cytoplasmic staining for VEGF-C was observed in neuroendocrine cells such as the alpha cells of the islets of Langerhans, prolactin secreting cells of the anterior pituitary, adrenal medullary cells, and dispersed neuroendocrine cells of the gastrointestinal tract. VEGF-D was observed in the innermost zone of the adrenal

cortex and in certain dispersed neuroendocrine cells. These results suggest that VEGF-C and VEGF-D have a paracrine function and perhaps a role in peptide release from secretory granules of certain neuroendocrine cells to surrounding capillaries.

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L24 2 DUP REMOVE L23 (8 DUPLICATES REMOVED)

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L24 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
2000247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) Vol. 267, No. 9, pp. 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-(VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D.

L24 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2
2000011413. PubMed ID: 10542248. Biosynthesis of vascular endothelial growth factor-D involves proteolytic processing which generates non-covalent homodimers. Stacker S A; Stenvers K; Caesar C; Vitali A; Domagala T; Nice E; Roufail S; Simpson R J; Moritz R; Karpanen T; Alitalo K; Achen M G. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia.. steven.stacker@ludwig.edu.au) . The Journal of biological chemistry, (1999 Nov 5) Vol. 274, No. 45, pp. 32127-36. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Vascular endothelial growth factor-D (VEGF-D) binds and activates the endothelial cell tyrosine kinase receptors VEGF receptor-2 (VEGFR-2) and VEGF receptor-3 (VEGFR-3), is mitogenic for endothelial cells, and shares structural homology and receptor specificity with VEGF-C. The primary translation product of VEGF-D has long N- and C-terminal polypeptide extensions in addition to a central VEGF homology domain (VHD). The VHD of VEGF-D is sufficient to bind and activate VEGFR-2 and VEGFR-3. Here we report that VEGF-D is proteolytically processed to release the VHD.

Studies in 293EBNA cells demonstrated that VEGF-D undergoes N- and C-terminal cleavage events to produce numerous secreted polypeptides including a fully processed form of M(r) approximately 21,000 consisting only of the VHD, which is predominantly a non-covalent dimer. Biosensor analysis demonstrated that the VHD has approximately 290- and approximately 40-fold greater affinity for VEGFR-2 and VEGFR-3, respectively, compared with unprocessed VEGF-D
. In situ hybridization demonstrated that embryonic lung is a major site of expression of the VEGF-D gene. Processed forms of VEGF-D were detected in embryonic lung indicating that VEGF-D is proteolytically processed in vivo.

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☐	L11	L10 and screening	60
☐	L10	L8 and VEGF-D	60

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☐	L8	L7 and screening	132
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	DB=DWPI; PLUR=YES; OP=OR		
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